

# EXHIBIT T

PATENT DOCKET 100/150C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of )

SHMUEL CABILLY ET AL. )

Serial No. 07/205,419 )

Filed: 06/10/88 )

For: RECOMBINANT )  
IMMUNOGLOBULIN )  
PREPARATIONS )

Art Unit: 183

Examiner: J. HULEATT

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GROUP 130

SUPPLEMENTARY PRELIMINARY AMENDMENT  
AND REQUEST FOR INTERFERENCE

Honorable Commissioner of Patents and Trademarks  
Washington, D.C. 20231

Sir:

Amendment

Please further amend this application by cancelling claims 53-67 and  
adding the following new claims:

61  
--67. A process for producing an Ig molecule or an immunologically  
functional Ig fragment comprising at least the variable domains of the Ig  
heavy and light chains, in a single host cell, comprising the steps of:

- (i) transforming said single host cell with a first DNA sequence  
encoding at least the variable domain of the Ig heavy chain  
and a second DNA sequence encoding at least the variable  
domain of the Ig light chain, and

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(ii) independently expressing said first DNA sequence and said second DNA sequence so that said Ig heavy and light chains are produced as separate molecules in said transformed single host cell.--

--68. The process according to claim 67 wherein said first and second DNA sequences are present in different vectors.--

--69. The process according to claim 67 wherein said first and second DNA sequences are present in a single vector.--

--70. A process according to claim 68 wherein the vector is a plasmid.-

--71. A process according to claim 70 wherein the plasmid is pBR322.-

--72. A process according to claim 67 wherein the host cell is a bacterium or yeast.--

--73. A process according to claim 72 wherein the host cell is *E. coli* or *S. cerevisiae*--

--74. A process according to claim 73 wherein the host cell is *E. coli* strain X1776.--

--75. A process according to claim 67 wherein the Ig heavy and light chains are expressed in the host cell and secreted therefrom as an immunologically functional Ig molecule or Ig fragment.--

--76. A process according to claim 67 wherein the Ig heavy and light chains are produced in insoluble form and are solubilized and

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- allowed to refold in solution to form an immunologically functional Ig molecule or Ig fragment.--
- 77. A process according to claim 67 wherein the DNA sequences code for the complete Ig heavy and light chains.--
- 78. A process according to claim 67 wherein said first or said second DNA sequence further encodes at least one constant domain, wherein the constant domain is derived from the same source as the variable domain to which it is attached.--
- 79. A process according to claim 67 wherein said first or said second DNA sequence further encodes at least one constant domain, wherein the constant domain is derived from a species or class different from that from which the variable domain to which it is attached is derived.--
- 80. A process according to claim 67 wherein said first and second DNA sequences are derived from one or more monoclonal antibody producing hybridomas.--
- 81. A vector comprising a first DNA sequence encoding at least a variable domain of an Ig heavy chain and a second DNA sequence encoding at least a variable domain of an Ig light chain wherein said first DNA sequence and said second DNA sequence are located in said vector at different insertion sites.--
- 82. A vector according to claim 81 which is a plasmid.--
- 83. A host cell transformed with a vector according to claim 81.--

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- C1*  
*Contd?*
- 84. A transformed host cell comprising at least two vectors, at least one of said vectors comprising a DNA sequence encoding at least a variable domain of an Ig heavy chain and at least another one of said vectors comprising a DNA sequence encoding at least the variable domain of an Ig light chain.--
- 85. The process of claim 67 wherein the host cell is a mammalian cell.--
- 86. The transformed host cell of claim 84 wherein the host cell is a mammalian cell.--

Specification Basis

Main claim 67 is based at least on section E.1.9 of the instant specification and the disclosure noted below:

<u>Claim 67</u>	<u>Specification page/line</u>
"A process for producing an Ig molecule	pages 8-9
or an immunologically functional Ig	page 13, lines 24-28;
comprising at least the variable domains	page 14, lines 1-12;
of the Ig heavy and light chains,	page 30, lines 10-15;
	page 43, lines 27-31

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in a single host, comprising the steps of page 23, lines 5-8 and lines  
28-34; page 22, lines 30-  
34;  
page 43, line 27 *et seq.*;  
original claims 43 and 50.

(i) transforming said single host cell page 22, lines 29-34; 23/8;  
with a first DNA sequence encoding at page 23, lines 5 and 8; page  
least the variable domain of the Ig 6, line 6; page 43, line 28  
heavy chain and a second DNA sequence *et seq.*; original claims 43  
encoding at least the variable domain of and 50.  
Ig light chain, and

(ii) independently expressing said first page 22, lines 30-34; page  
DNA sequence and said second DNA sequence 23, lines 10-12 and lines 28  
so that said Ig heavy and light chains are 34; page 44, lines 5-19; and  
produced as separate molecules in said page 45, line 34.  
transformed single host cell.

The basis for the remaining new claims is at least as follows:

<u>Claim</u>	<u>Specification page/line</u>
68	page 22, lines 32-33; section E.1.9

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69, 70, 81, 82 and 83	page 22, lines 33-34; section E.1.9
71	page 16, line 15; section E.1.9
72, 73, 74	pages 15-16; section E.1.9
75	page 23, lines 21-34; section E.1.9
76	page 23, lines 18-21; sections D.2, E.5 and E.1.9
77	page 24, lines 2-3; section E.1.9
78	page 11, line 27 - page 12, line 26; section E.1.9
79	page 11, line 27 - page 12, line 26; section D.6; section E.1.9
80	page 21, line 7; section E.1.9
84	Same as claim 67
85 and 86	page 18, lines 1-30

Interfering Patent

New claims 67 - 84 (excepting claims 70, 71, 73, 74, 76 and 79) are verbatim replicates of claims 1- 18 of U.S. patent 4,816,397 to Boss *et al.* ("Boss"). Attached as Appendix 1 is a proposed count for interference. The proposed count is identical to claim 1 of the Boss patent. Claims 1-18 of Boss, all of the claims therein, correspond to the proposed count. Claims 67-86 of the instant application, all pending

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claims, correspond to the proposed count.

The present application claims the benefit under 35 USC 120 of U.S.S.N. 06/483,587, filed April 8, 1983. The Boss patent claims foreign priority under 35 USC 119 of a United Kingdom application filed March 25, 1983. Thus, the present application has an effective filing date subsequent to the filing date of the foreign application. In accordance with the instructions in the first paragraph of MPEP 2308.01 and the last sentence of the sixth paragraph of MPEP 2309.02, Boss should not be accorded the benefit of the foreign application in the Declaration of Interference. Instead, Boss should be limited to their actual U.S. filing date of November 14, 1984, or at the earliest, March 23, 1984, the international filing date of the PCT application which ultimately matured into the Boss patent. Accordingly, the present applicants should be designated the senior party.

Reference to Related Patent

The parent to the instant application, U.S.S.N. 06/483,587, has issued as U.S. patent 4,816,567 (attached as Appendix 2) ("Cabilly"). The Cabilly patent is directed to novel forms of antibodies termed chimeric immunoglobulins, as well as vectors and methods for making same. These antibodies are interspecies chimeras of variable and constant region

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chimeras. While the method of newly submitted claim 67 (and Boss) can be used for making such chimeric immunoglobulins, it is not necessary to use this method since the chimeric immunoglobulin chains can be produced in host cells transformed only with heavy or light chain, but not both as is called for in claim 67. Similarly, claim 67 is applicable to all forms of antibodies, and not only chimeric forms. The pending claims and those of Boss accordingly are cross-dominating but are not directed to the same patentable invention. It also should be noted that Cabilly is completely devoid of any teaching to produce interspecies variable-constant region chimeras. The only possible relevant disclosure in the Cabilly patent is found at column 4, lines 59-60, where interclass chimeras are suggested. Immunoglobulins are divided into different isotypes or classes, but this has nothing to do with what species the immunoglobulins are from. Claim 13 of the Cabilly patent calls for a constant chain "derived from a different source" than the variable domain. The specification does not define "source", but it must be interpreted in light of the specification as referring to interclass chimeras. Thus, the Cabilly patent and the Boss patent are directed to separate patentable inventions. Presumably, as much has already been recognized by the Office in deciding to grant both the Boss patent and the Cabilly patent.

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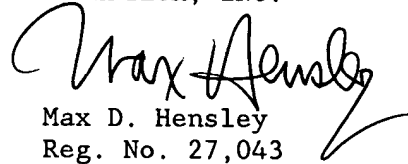
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Response to Restriction Requirement Mailed March 6, 1990

In response to this restriction requirement, applicants elect the invention of Group I with traverse. The newly submitted claims herein fall within Group I and should be considered in place of claims 53-63 and 65-66, which have been cancelled. As an aside, the Examiner is thanked for her reminder to file a certificate of correction in the parent issue patent. This will be done in due course.

Respectfully Submitted  
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Appendix 1

Proposed Count

A process for producing an Ig molecule or an immunologically functional Ig fragment comprising at least the variable domains of the Ig heavy and light chains, in a single host cell, comprising the steps of:

- (i) transforming said single host cell with a first DNA sequence encoding at least the variable domain of the Ig heavy chain and a second DNA sequence encoding at least the variable domain of the Ig light chain, and
- (ii) independently expressing said first DNA sequence and said second DNA sequence so that said Ig heavy and light chains are produced as separate molecules in said transformed single host cell.

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